

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 25 is requested to be cancelled without prejudice or disclaimer.

Claims 1-24 and 26-39 are currently being amended. These amendments are made to place the claims in U.S. format and correct typographical errors. In addition, these amendments are discussed below in Sections II and III. Support for these amendments can be found throughout the specification as-filed, including the original claims. No new matter is being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-46 are now pending, and claims 15-17, 21-24, 29, 31-38, and 40-46 are withdrawn from consideration. At least claims 15-17, 21-24, 29, and 31-38 should be rejoined, because they are the same statutory class of invention as claim 1, and unity of invention is believed to exist. Thus, claims 1-14, 18-20, 25-28, 30, and 30 are pending and being examined on the merits, and at least claims 1-24 and 26-39 should be examined together.

I. Restriction/Election

The Examiner notes Applicants' election of Group I, claims 1-39, and further election of lacto-N-neotetraose and polylactosamine as the oligosaccharides, lactose as the exogenous precursor, and β -1,3-N-acetyl-glucosaminyl-transferase and β -1,4-galactosyl-transferase as the

recombinant genes. Accordingly, the Examiner withdraws claims 15-17, 21-24, 29, 31-38, and 40-46.

Applicants note the previously imposed restriction requirement and proceed with prosecution of the elected subject matter. Applicants, nevertheless, request rejoinder wherever permitted, as noted above.

II. Claim Objections

The Examiner has made a number of rejections based on “informalities” in the claims. Applicants do not necessarily acquiesce to the Examiner’s arguments but make the amendments discussed below for the sake of expediting prosecution.

A. Claim 1 – “and”

The Examiner objects to claim 1, because the Examiner argues that an “and” should be inserted between steps (i) and (ii).

Applicants have amended claim 1 to insert “and” where suggested by the Examiner. Accordingly, Applicants respectfully request withdrawal of this ground of objection.

B. Claims 7 & 9 – “Chosen From”

The Examiner objects to the recitation of “chosen from” in claims 7 and 9 and suggests that the phrase be replaced with “selected from the group consisting of.”

Applicants have amended claim 7 and 9 to recite “selected from the group consisting of,” as suggested by the Examiner. Accordingly, Applicants respectfully request withdrawal of this ground of objection.

C. Claim 39 – “a said”

The Examiner objects to claim 39 as being grammatically incorrect for reciting “a said.”

Applicants have amended claim 39 to recite “said” instead of “a said.” Accordingly, Applicants respectfully request withdrawal of this ground of objection.

D. Claim 25 – Dependency

The Examiner objects to claim 25 as an allegedly improper dependent claim. According to the Examiner, claim 25 does not further limit its parent claim, claim 1, because claim 25 “recites a limitation already required in Claim 1 and thus is not further limiting.” Office action at 3.

Applicants have cancelled claim 25. Thus, this amendment renders the objection moot.

III. Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 1-14, 18-20, 25-28, 30, and 39 stand rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. Each of the specific rejections is addressed below.

A. Claims 1 and 2 – “Said Precursor Being Involved In The Biosynthetic Pathway Of Said Oligosaccharide”

Claims 1 and 2 stand rejected as allegedly indefinite for reciting “said precursor being involved in the biosynthetic pathway of said oligosaccharide.” According to the Examiner, “it is unclear how this phrase modifies the scope of precursors recited as it is unclear how a precursor could not be involved in the biosynthetic pathway of the oligosaccharide.” Office action at 3-4.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 1 remove the recitation “said precursor being involved in the biosynthetic pathway of said oligosaccharide” and have amended claim 2 to remove the recitation “involved in the

biosynthetic pathway of said oligosaccharide.” Accordingly, this amendment renders the rejection moot.

B. Claim 2 – “Said Enzyme Being Identical To Or Different That The Enzyme Used In The Method Described Above”

Claim 2 stands rejected as allegedly unclear for reciting “said enzyme being identical to or different that the enzyme used in the method described above.” According to the Examiner, “it is unclear how the claim further limits claim 1 if the enzyme is identical to the enzyme in Claim 1.” Office action at 4. In addition, the Examiner argues that is unclear whether the method of claim 1 is referred to or some other method. Applicants respectfully traverse this ground of rejection.

Claim 2 further limits claim 1, because it recites “at least one gene encoding an enzyme capable of modifying an endogenous precursor” (emphasis added). On the other hand, claim 1 recites “at least one recombinant gene encoding an enzyme capable of modifying said exogenous precursor” (emphasis added). Thus, claim 2 recites “at least one gene encoding an enzyme capable of modifying” both “an endogenous precursor” and “an exogenous precursor.” “The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. 112 is whether the dependent claim includes every limitation of the claim from which it depends. The test is not one of whether the claims differ in scope.” MPEP § 608.01(n)(III). Claim 2 includes every limitation of claim 1. Thus, claim 2 is a proper dependent claim.

While not acquiescing in the propriety of the rejection, claim 2 has been amended to recite “the enzyme of claim 1” rather than “the enzyme used in the method described above.” Thus, claim 2 is clear as to the method referred to.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

C. Claim 2 – “Said Cell Lacks Any Enzymatic Activity Liable To Degrade Said Precursor”

Claim 2 stands rejected as allegedly unclear for reciting “said cell lacks any enzymatic activity liable to degrade said precursor.” According to the Examiner, it is unclear whether “said precursor” refers to the endogenous precursor or the exogenous precursor.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 2 to make clear that the precursor being referred to is the endogenous precursor. Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

D. Claim 4 – “A Bacterium, Preferably Of *Escherichia Coli* Type”

Claim 4 stands rejected as allegedly indefinite for reciting “a bacterium, preferably of *Escherichia coli* type.” According to the Examiner, it is unclear whether or not the claim requires the cell be an *E. coli* cell.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 4 to remove the recitation “preferably of *Escherichia coli* type.” Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

E. Claims 12 – “Is At Least 30% Less, Preferentially 50% And Preferably 60%”

Claim 12 stands rejected as allegedly indefinite for reciting “is at least 30% less, preferentially 50% and preferably 60%.” According to the Examiner, “it is unclear whether the features following ‘preferentially’ and ‘preferably’ are (a) merely exemplary and therefore not required, or (b) a required feature of the claim.” Office action at 4.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 12 to remove the recitation “preferentially 50% and preferably 60%.” Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

F. Claim 14 – Carbohydrate Nature, Preferably Of Oligosaccharide Nature

Claim 14 stands rejected as allegedly unclear for reciting “carbohydrate nature, preferably of oligosaccharide nature.” According to the Examiner, “it is unclear whether the feature following ‘preferably’ is (a) merely exemplary and therefore not required, or (b) a required feature of the claim.” Office action at 5.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 12 to remove the recitation “preferably of oligosaccharide nature.” Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

G. Claim 19 – “Preferably”

Claim 19 stands rejected as allegedly indefinite for reciting “preferably.” According to the Examiner, “it is unclear whether the features following ‘preferably’ are (a) merely exemplary and therefore not required, or (b) a required feature of the claim.” Office action at 5.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 19, so the claim no longer recites “preferably.” Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

H. Claims 20 & 27 – “Said Active Transport”

Claims 20 and 27 stand rejected as “confusing” for reciting “said active transport.” The Examiner argues that the claims are unclear, because the parent claims of claims 20 and 27 do not require “active” transport.”

While not acquiescing in the propriety of the rejection, Applicants have amended claims 20 and 27 to no longer recite “active.” Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

I. Claim 30 – “Said Substrate” & “Said Inducer”

Claim 30 stands rejected as allegedly indefinite for reciting “said substrate” and “said inducer,” because the Examiner argues that the terms lack antecedent basis in claim 1, claim 30’s parent claim.

Applicants have amended claim 30, so the claim terms have proper antecedent basis. Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

IV. Claim Rejections – 35 U.S.C. § 112, first paragraph

A. Written Description

Claims 1-14, 18-20, 25-28, 30, and 39 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking written description support. According to the Examiner, the specification does not provide adequate written description of the genes, precursors, and types of cells that can be used to practice the claimed invention. Office Action at 6-7. Applicants respectfully traverse this ground of rejection.

The specification contains a sufficient description of the genes, precursors, and types of cells that can be used to practice the claimed invention to show possession of the claimed invention. Specifically, the specification lists a number of genes that can be used, including a description of the products encoded by the genes. *See e.g.*, page 16, lines 15-34. In addition, the specification notes that genes encoding the enzymes involved in the synthetic pathway of oligosaccharides are known in the art and cites representative literature. *See e.g.*, page 2, lines 12-17; page 3, lines 13-19. page 9, lines 16-26. Thus, the specification states that suitable genes are known in the art and provides a number of specific examples.

The specification also contains a list of precursors that can be used, such as 4-O-β-D-galactopyranosyl-D-fructofuranose (lactulose), 3-O-β-D-galactopyranosyl-D-arabinose, allyl-β-

D-galactopyranoside, melibiose, raffinose, allyl- α -D-galactopyranoside, and sucrose. *See e.g.*, page 11, lines 6-39; page 13, lines 8-30. Indeed, oligosaccharide biosynthetic pathways are well-known in the art. Thus, the specification supplements the knowledge of one of skill in the art by listing a number of specific precursors that can be used in the claimed method.

Finally, the specification lists a number of cells that can be used to practice the claimed invention. Indeed, the specification states that the cells can be selected from *Escherichia coli*, *Bacillus subtilis*, *Campylobacter pylori*, *Helicobacter pylori*, *Agrobacterium tumefaciens*, *Staphylococcus aureus*, *Thermophilus aquaticus*, *Azorhizobium caulinodans*, *Rhizobium leguminosarum*, *Neisseria gonorrhoeae*, *Neisseria meningitis*, *Saccharomyces cerevisiae*, *Saccharomyces pombe* and *Candida albicans*. *See* page 6, lines 1-19. In addition, the production of oligosaccharides in host cells is known in the art.

The description of genes, precursors, and types of cells that can be used to practice the claimed invention is adequate in light of the knowledge of one of skill in the art. Indeed, the specification provides lists of suitable genes, precursors, and types of cells, and specific examples of suitable genes, precursors, and types of cells. Recently, the Federal Circuit addressed whether or not a specification provided adequate support for a well-known genus of host cells recited in the claims. *Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003). The court concluded that “one of skill in the art could ‘visualize or recognize the identity of the members of the genus’” reasoning that “the claims terms at issue [] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.” *Id.* In *Amgen*, the specification described producing the recombinant protein in only two species of the recited genus. *Id.* Like in *Amgen*, the genres at issue here are well-known in the art. Moreover, the specification provides far more than two examples. Accordingly, the specification adequately describes the claimed genres.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

B. Enablement

Claims 1-4, 8-13, 25, 27, and 39 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. According to the Examiner, the specification does not provide adequate guidance to allow one of skill in the art to practice the claimed invention using any genes, precursor, and cell type. Applicants respectfully traverse this ground of rejection.

The specification contains sufficient guidance to allow one of skill in the art to practice the claimed invention without undue experimentation. Indeed, the specification describes a number of genes, precursors, and cell types that can be used, as noted above. In addition, the specification contains extensive guidance on how to use these particular components in using the claimed invention. *See* page 6, line 1 – page 21, line 29. The specification contains working examples verifying the teachings of the specification. These working examples employ two strains of *E. coli*. and several different genes to produce allyl β -D-galactopyranoside, allyl-N-acetyl- β -D-glucosaminide, trisaccharide 4-O-[3-O-(2-acetamido-2-deoxy- β -D-glucopyranosyl)- β -D-galactopyranosyl]-D-glucopyranose, (β -D-GlcNAc-[1 \rightarrow 3]- β -D-Gal-[1 \rightarrow 4]-D-Glc), lacto-N-neo-tetraose, polylactosamine, allyl 3-O-(2-acetamido-2-deoxy- β -D-glucopyranosyl)- β -D-galactopyranoside, (β -D-GlcNAc-[1 \rightarrow 3]- β -D-Gal-1 \rightarrow O-allyl), β -D-Gal-[1 \rightarrow 4]- β -D-GlcNAc-1 \rightarrow O-allyl, 3'-sialyllactose (α -NeuAc-[2 \rightarrow 3]- β -D-Gal-[1 \rightarrow 4]- β -D-Glc), and analoges of these oligosaccharides. Thus, the specification contains extensive guidance to allow one of skill in the art to practice the claimed invention.

The Examiner contends that it would constitute undue experimentation to practice the claimed invention using the entire genus genes, precursors, and host cells. For example, the Examiner argues that “[t]he claims recite methods of making any oligosaccharide in any bacterium, requiring the use of an enormous number of different glycosyltransferase genes.

However, “[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” MPEP § 2164.01 (citations

omitted). Here, glycosyltransferase genes are known in the art and methods of genetic engineering are known in the art. Thus, making a wide variety of oligosaccharides using the claimed invention may require experimentation, or even complex experimentation, such experimentation is not undue. Indeed, the specification provides guidance as to how to practice the claimed invention in a variety of embodiments. Accordingly, the experimentation required is not undue.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

V. Claim Rejections – 35 U.S.C. § 102

A. Claims 1-8, 14, 18, 19, 25, and 26 – Koizumi

Claims 1-8, 14, 18, 19, 25, and 26 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Koizumi *et al.*, NATURE BIOTECHNOLOGY 16:847-850 (1998). According to the Examiner, Koizumi teaches “the production of the trisaccharide globotriose in a LacZ⁻ *E. coli* transformed with the *Neisseria gonorrhoeae* LgtC gene encoding an α -1,4-galactosyltransferase from exogenously provided lactose (see page 848-849).” Office Action at 11. Applicants respectfully traverse this ground of rejection.

1. Summary of Koizumi

Koizumi describes what is known in the art as a bacterial coupling system. Specifically, Koizumi employs three different organisms to produce globotriose: (1) one organism produces UTP (*C. ammoniagenes*); (2) one organism produces UDP-Gal (*E. coli* engineered with *galT*, *galK*, *galU* and *ppa*) using the UTP; and (3) one organisms produces globotriose from lactose and UDP-Gal (*E. coli*. engineered with *lgtC*). Koizumi, pg. 847, right col. On the other hand, the present invention allows the synthesis of the oligosaccharide and the regeneration of the sugar-nucleotide in the same organism.

2. Koizumi Does Not Teach Or Suggest The Claimed Invention

Koizumi does not teach or suggest a method of producing an oligosaccharide in cells in culture, as claimed. Indeed, Koizumi's system requires that the *E. coli* must internalize both lactose and UDP-Gal. However, there is no permease for UDP-Gal. Accordingly, Koizumi teaches internalizing the UDP-Gal by a chemical treatment comprising treating the cells with a surfactant and xylene. Koizumi, pg. 848, left col., lines 9-12. This chemical treatment breaks the proton motive force across the cytoplasmic membrane thereby destroying the activity of lactose permease, which functions as an H⁺/lactose symport mechanism. Thus, the lactose is internalized by simple diffusion. Accordingly, Koizumi's method requires killing the cells to permit the entry of UDP-Gal, unlike the present invention where the oligosaccharide is produced by living cells in culture.

In other words, Koizumi requires several steps to produce oligosaccharide. First, bacteria are grown, *i.e.* cultured, to a sufficient biomass. Second, the bacteria are harvested and permeabilized, which kills the cells. Finally, the permeabilized cells are incubated with precursors to produce oligosaccharides. On the other hand, the present invention provides a method using live cells producing oligosaccharide during the growth of the cells. Thus, the present invention provides a single step method that does not require multiple organisms and multiple steps to produce oligosaccharide.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

B. Claim 20 – Koizumi

Claim 20 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over Koizumi. Applicants respectfully traverse this ground of rejection.

As discussed above in Section V(A), claim 1 is novel over Koizumi. Claim 20 is dependent on claim 1. Accordingly, claim 20 is novel over Koizumi.

For at least this reason, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

VI. Claim Rejections – 35 U.S.C. § 103

A. Claims 27, 28, & 39 – Koizumi

Claims 27, 28, and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Koizumi. The Examiner notes that Koizumi does not teach the use of IPTG or the production of radiolabelled oligosaccharide. However, the Examiner argues that the use of IPTG and radiolabelled oligosaccharides are well-known in the art and would have been obvious.

Applicants respectfully traverse this ground of rejection.

As discussed above in Section V(A), Koizumi fails to teach each and every element of claim 1. Accordingly, Koizumi also fails to teach each and every element of the claims dependent on claim 1, including claims 27, 28, and 39. Thus, Koizumi cannot render obvious claims 27, 28, and 29. *See* MPEP § 2143.

For at least this reason, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

B. Claims 9-13 – Koizumi in view of Bettler

Claims 9-13 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Koizumi in view of Bettler *et al.*, GLYCOCONJUGATE JOURNAL 16:205-212 (1999). The Examiner notes that Koizumi does not teach the production of globotriose using high cell density culture conditions or the use of glycerol as the carbon source. The Examiner cites Bettler to remedy these deficiencies. Applicants respectfully traverse this ground of rejection.

As noted above in Section V(A), Koizumi fails to teach each and every element of the claimed invention. Bettler does nothing to remedy this deficiency. Accordingly, Koizumi and Bettler, alone or in combination, fail to teach or suggest the claimed invention.

For at least this reason, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

C. Claim 30 – Koizumi in view of Johnson and Gotschlich

Claim 30 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Koizumi in view of Johnson, GLYCOCONJUGATE JOURNAL 16(2):141-46 (1999) and WO 96/10086 to Gotschlich. The Examiner notes that Koizumi “does not teach the production of laco-N-neotetraose from lactose using a bacterium transformed with a β -1,3-N-acetylglucosaminyltransferase and a β -1,4-galactosyltransferase gene.” Office Action at 15. Johnson and Gotschlich are cited as remedying these deficiencies. Applicants respectfully traverse this ground of rejection.

As noted above in Section V(A), Koizumi fails to teach each and every element of the claimed invention. Johnson and Gotschlich, either alone or in combination, fail to remedy this deficiency. Accordingly, the claimed invention cannot be rendered obvious by Koizumi in view of Johnson and Gotschlich.

For at least this reason, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date

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